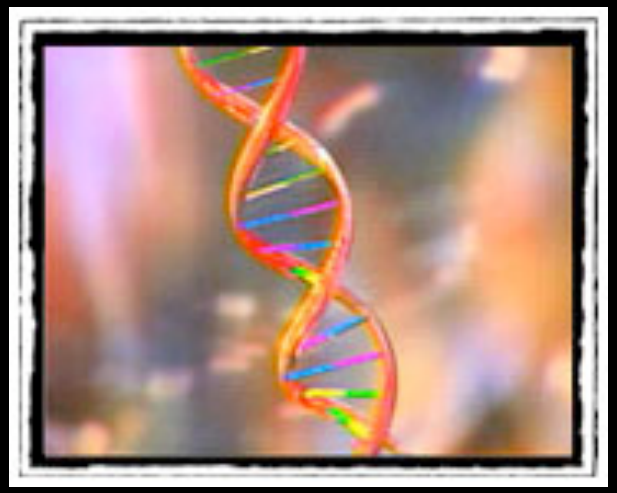
Genetics of Complex Diseases

Governor's Vision Conference: Personalized Medicine

Salt Lake City, UT
December 5-6, 2006



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Disclosure

Aravinda Chakravarti is a paid member of the Scientific Advisory Board of Affymetrix. This potential conflict of interest is managed by the policies of Johns Hopkins University School of Medicine

Outline of Talk

1. Genetics of complex disease
2. Principles of genetic variation & association mapping
3. International HapMap Project
4. Finding disease genes by whole-genome scanning
5. Genes for QT-interval and Sudden Cardiac Death

Genetics of Complex Disease

THE HUMAN DISEASE BURDEN:

1.5% from single gene disorders (sickle cell anemia, phenylketonuria,etc.)

3.5% from chromosomal anomalies (Down, Turner, Klinefelter syndromes, etc,)

The vast majority have familial aggregation, genetic etiology but complex inheritance

Single gene inheritance of disease is the exception not the rule

THE CURRENT GENETIC PARADIGM:

Newborn screening to identify preventable genetic outcomes

Diagnosis based on phenotype (dysmorphology) and family history

Molecular (DNA-based) and chromosomal diagnosis

Protein replacement therapy

Reproductive choices and genetic counseling

THE DNA REVOLUTION

The Secret of Life

Cracking the DNA code has changed how we live, heal, eat and imagine the future. By Nancy Gibbs

ANY 4-YEAR-OLD WHO LIKES LADYBUGS AND LIGHTNING BOLTS CAN TELL YOU THAT LIFE IS wildly beautiful as far as the eye can see. But it took the geniuses of our time to reveal how bea see it at all—in the molecular worksho nd Francis Crick did not dis- cover th hich means they unveiled its power as , it would reach 6 ft. in length, a code b G and C. Fold it back up, and it shrink y one of our 100 trillion cells,

James Fixx (1932-1984)

Was Jim Fixx's Sudden Cardiac Death preventable?

Photo-Illustration for TIME by Glen Wexler

Genetics is pointing the way to generalized personalized medicine…
the practice of medicine embracing human genetic individuality

3 P's: personalized, predictive & preventive medicine for disease susceptibility and treatment response

Complex inheritance: An Hypothesis

Complex (non-mendelian) inheritance arises
from the accumulation of
common polymorphisms with
small-to-modest allelic effects
at multiple genes

Common variants underlying disease can be identified *a priori*

Principles of Genetic Variation

Classification of Genetic Variation by Type

SNPs (single nucleotide polymorphism):85%

AAGTCGATTGACCGAATTAATTAATTGCGGT
AAGTCGATTGATCGAATTAATTAATTGCGGT

INDELs (insertions/deletions), CNVs (copy number variants),micro/macrosatellites: 10%

AAGTCGATTGACCGAATTAATTAATTGCGGT
AAGTCGATTGACCG -------AATTAATTGCGGT

Inversions, segmental rearrangements: 5%

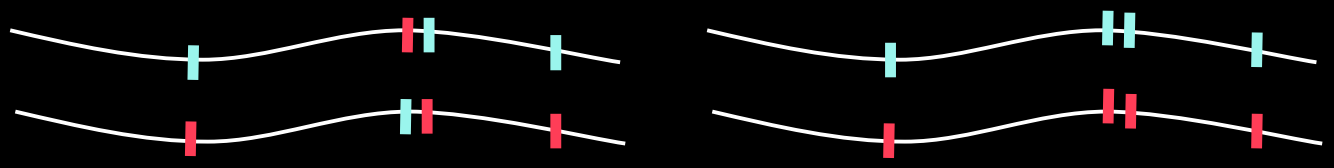
Characteristics of SNPs

Genetic differences occur about 1 in 1,000 nucleotides for any two genomes compared

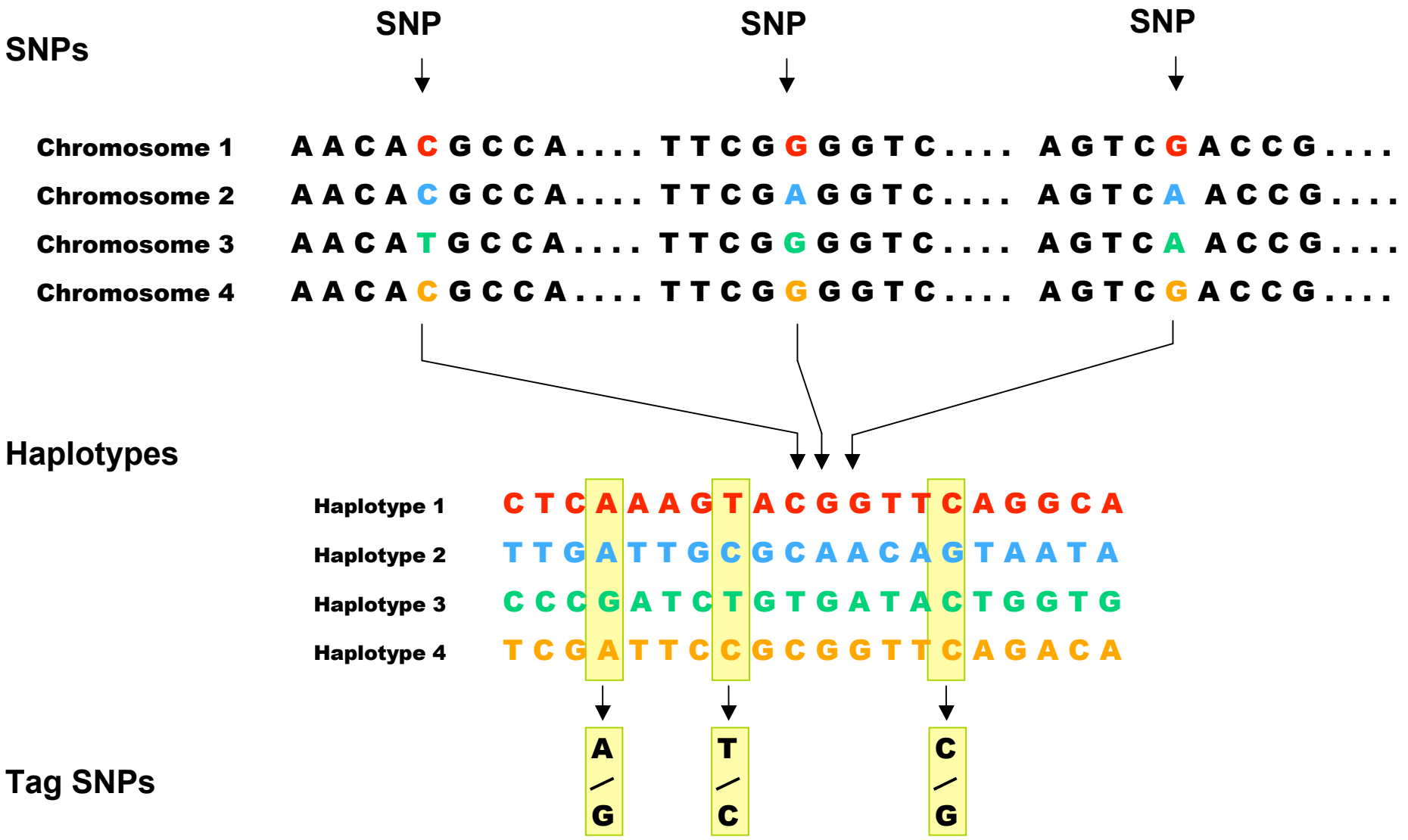
In a genome of 3 billion nucleotides that's 3 million variants per individual

Some of these variants are specific to individuals while others are common to many

Overall 10 million SNPs exist…they occur in specific patterns called haplotypes (arrangement of SNPs on a chromosome)



DNA sequence, SNPs and the concept of tagSNPs



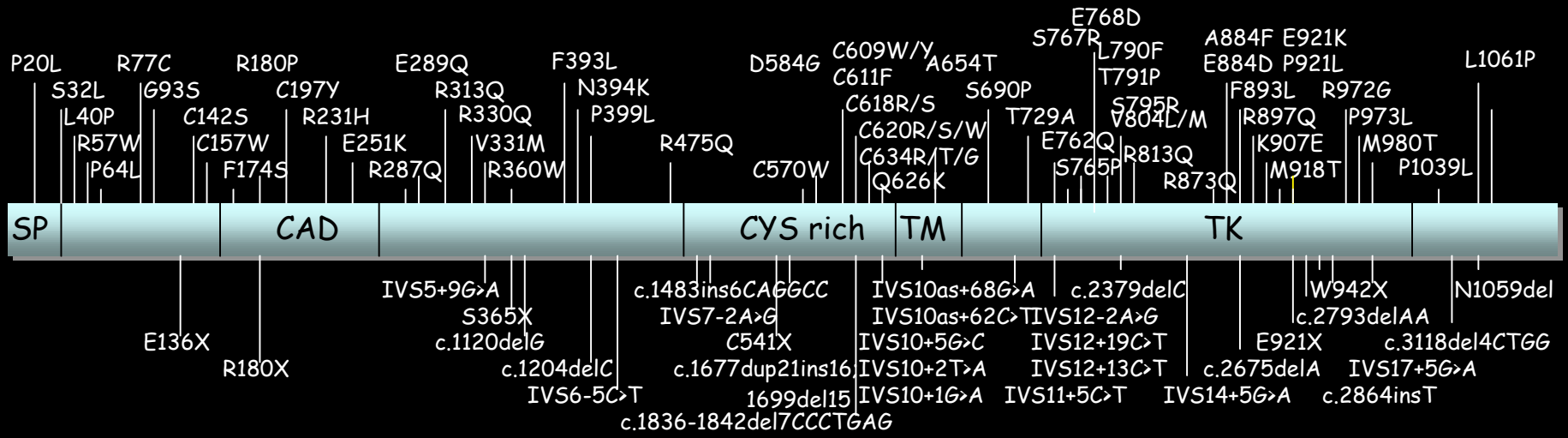
Principles of Association mapping

Disease genes that define host-specific differences need to be identified by:

Family-based linkage studies
Population or family-based association studies
Large-scale DNA sequencing
Biomarker (RNA, protein) discovery

Each of these methods are critical

RET mutational spectrum*: rare mutations everywhere

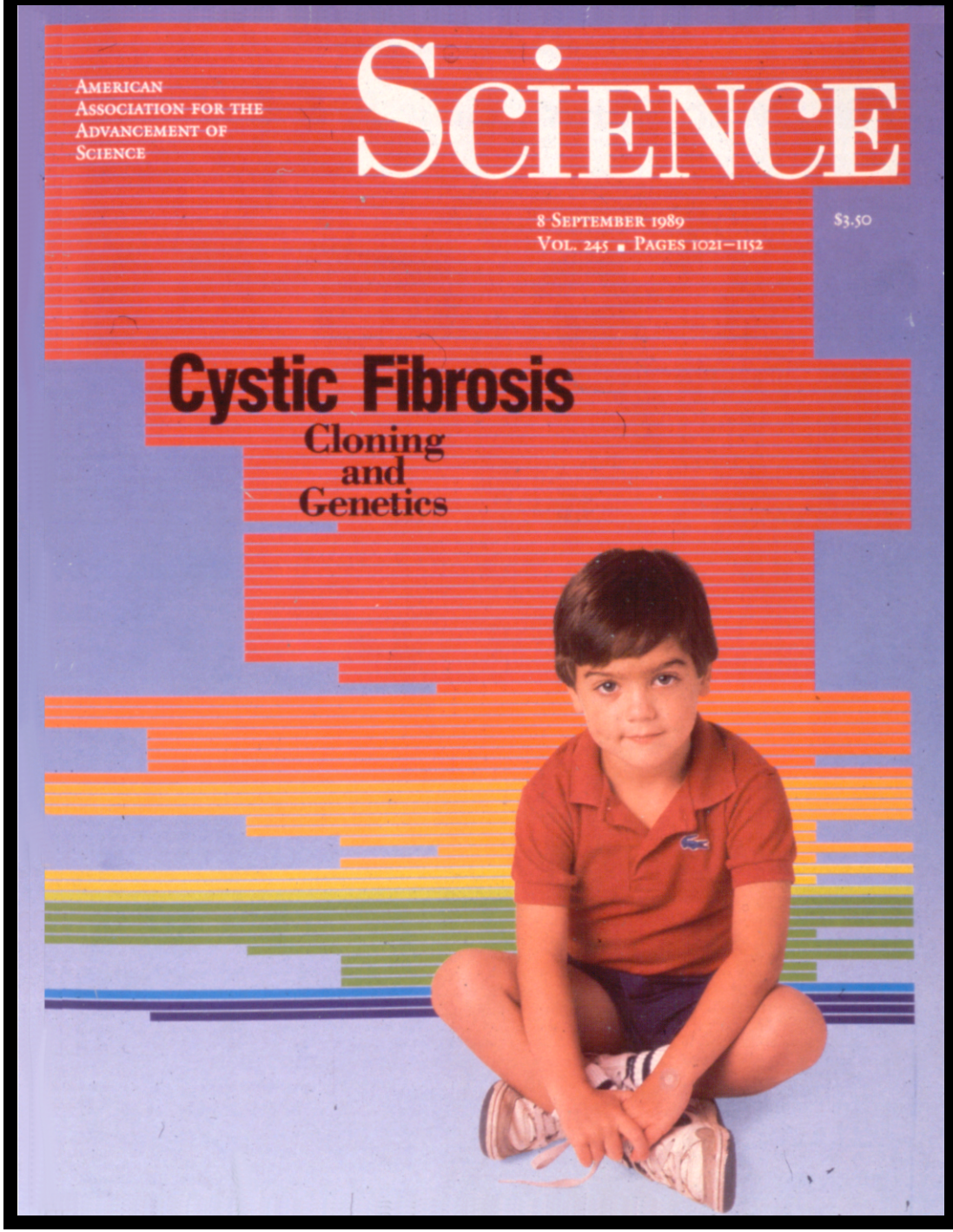


*Largely (but not exclusively) syndromic and severe HSCR

Whenever a mutation has a single origin it can be identified individually or through its association with nearby markers…

…surrogates by virtue of being associated in the population through shared genetic history

linkage disequilibrium (LD) mapping



CFTR cloning assisted by LD Mapping

ΔF508 ~ 70% of all mutants

ΔF508 modifies the pancreatic sufficiency phenotype

Common Gene Variation in Complex Disease

- Case-control studies, comparing the frequencies of common gene variants can identify susceptibility and protective alleles
- Some have multiple identified genes (*)

Phenotype	Gene	Variant
Peptic ulcer	ABO	B
IDDM*	HLA	DR3,4
Alzheimer dementia	APOE	E4
Deep venous thrombosis	F5	Leiden
Falciparum malaria*	HBBE	β^S
AIDS*	CCR5	Δ32
Colorectal cancer	APC	3920A
NIDDM*	PPARγ	12A

Why whole genome association studies?

1) We remain woefully ignorant of the fundamental molecular pathophysiology of complex human diseases.

2) The genetic paradigm identifies genes in the face of ignorance of the pathways involved.

3) Unbiased search across the whole genome.

4) Association studies are (but linkage analysis are not*) efficient for mapping disease genes when the underlying alleles are common (>5%).

(*Success in linkage studies depends on segregation of trait genes in families…segregation frequency decreases when disease alleles are common and many trait genes are homozygotes.)

International HapMap Project

The International HapMap Consortium
A Haplotype Map of the Human Genome.
Nature 437: 1299-1320, 2005.

Haplotype Map of the Human Genome

Goals: provide genotyping information to support efficient and well-powered genetic association studies of human disease

- Define patterns of genetic variation across human genome
- Guide selection of SNPs efficiently to "tag" common variants
- Public release of all data (assays, genotypes): www.HapMap.org

Phase I: 1.3 M markers in 269 people (1SNP/5kb at 5%+)
Phase II: +2.6 M markers in 270 people(1SNP/1kb at 5%+)

Finding disease genes: whole-genome association studies

Why now?

1) Human genome reference sequence is complete.

2) Improving annotation of function through experiment and evolutionary conservation.

3) International HapMap Phase II project nearing completion (>3.5m validated SNPs genotyped in 270 individuals across 4 human populations: www.HapMap.org).

4) Availability of large-scale and accurate genotyping and computing technologies.

Designing whole genome association studies: Phenotype

1) Susceptibility or protection; disease onset and progression; target organ damage and complications; adverse drug response (pharmacogenetics).

2) Qualitative or quantitative measures; reliability and accuracy.

3) Demonstrated heritability (twin studies or family studies).

Designing whole genome association studies: Samples

1) Family-based (parent-child trios or sibships) or population-based (case-control or case-cohort) studies.

2) Sampling the extremes of the population distribution of a quantitative phenotype.

3) One stage or multi-stage designs.

4) Replication study samples.

Genome-wide Association Studies: Recent Successes in Complex Diseases & Traits

Class variant: variants within a functional class (coding; non-synonymous)

LFA (lymphotoxin α) in myocardial infarction

IFIH1 (interferon induced helicase) in type 2 diabetes

Genome-wide: function-agnostic survey of the entire genome

CFH (complement factor H) in age-related macular degeneration

INSIG2 (insulin-induced gene 2) in BMI/obesity

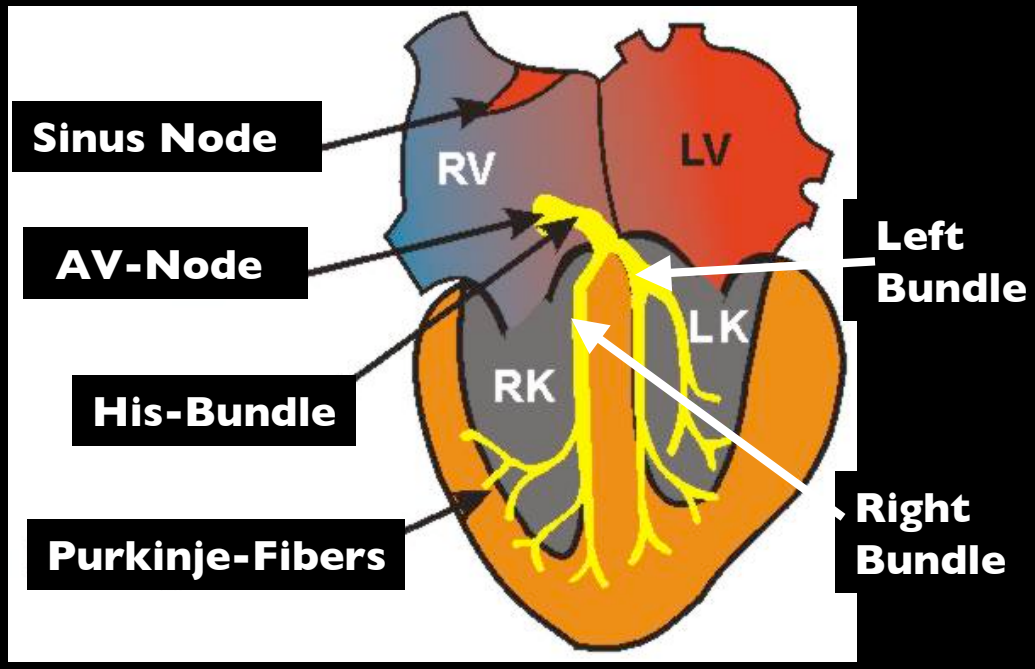
NOS1AP (nitric oxide synthase adapter protein) in the QT-interval/Sudden Cardiac Death

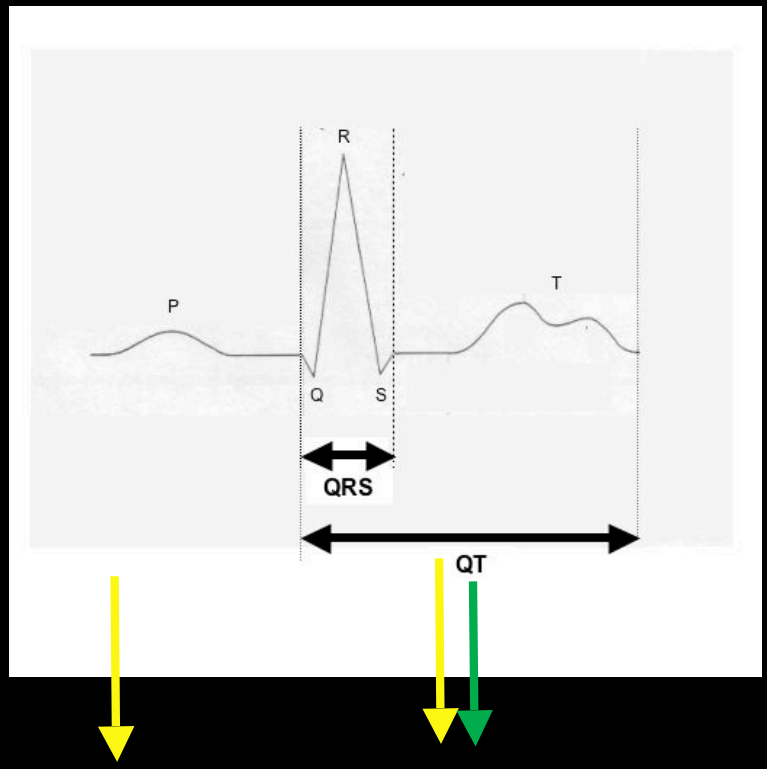
Genes underlying the QT-interval and Sudden Cardiac Death

QT interval: SCD intermediate trait?

Extremes of QT interval, from rare mutations, lead to sudden death (LQTS, SQTS)

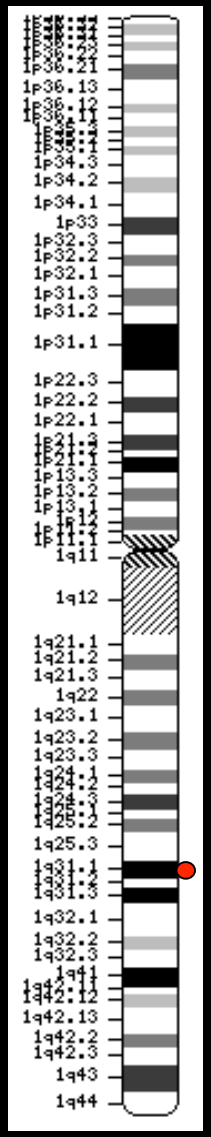
Correlation between QT interval and increased CVD mortality in the general population





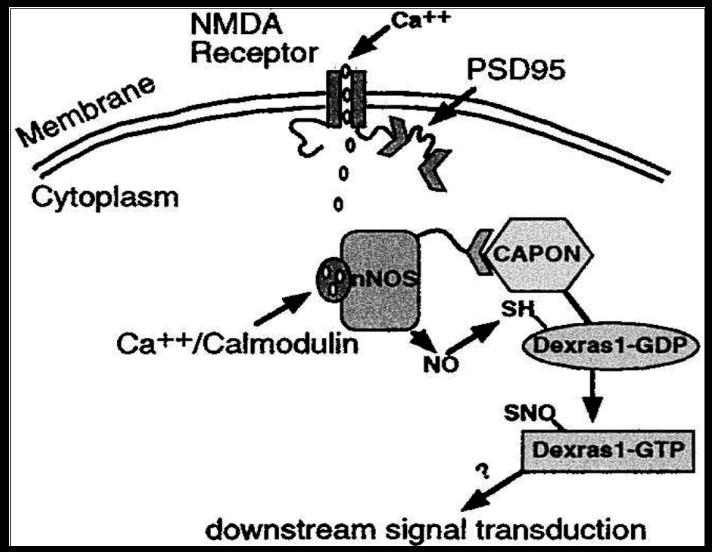
NOS1AP (*CAPON*) affects the QT-interval

Chr1



CAPON/ NOS1AP
4.9 ms
(λ ~1.7)
36%
1.2%
P~10^{-7}

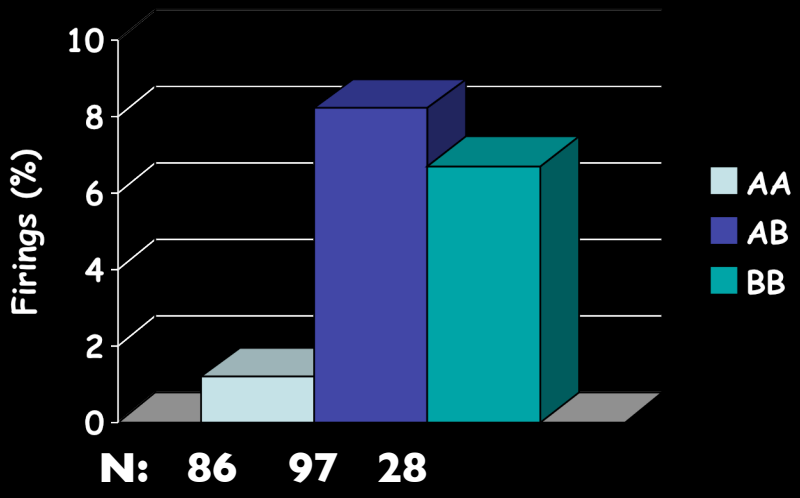
- Carboxy-terminal PDZ ligand of nNOS
- Expressed in cardiomyocytes
- Competes with PSD95 to interact with nNOS through the PDZ domain



CAPON's role in ICD Firings & SCD

211 cases

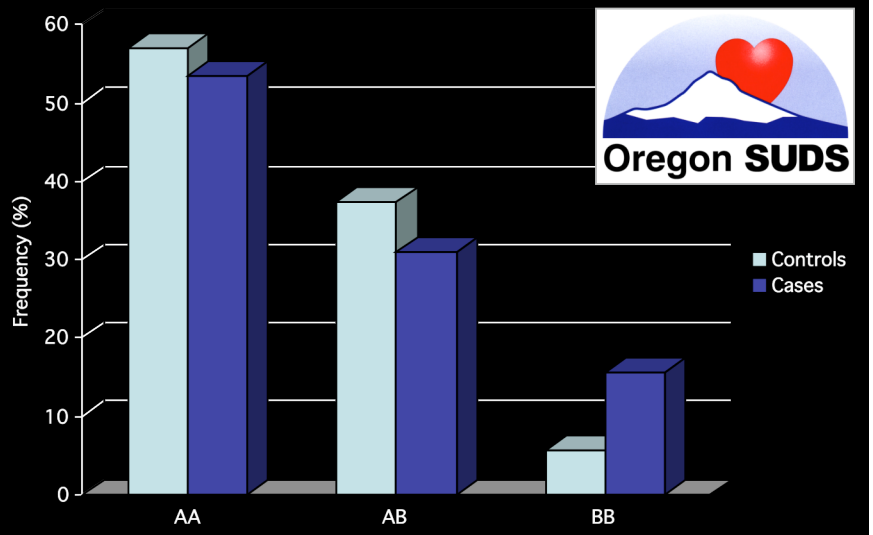
P<0.026



Reynolds ICD Registry
Firing = VT/VF

71 cases, 107 controls

P<0.025



Oregon SUDS
(witnessed, un-witnessed & non-resuscitated cardiac arrests)

B = TTGC haplotype associated with increased QT_cRAS
A = all other haplotypes

Whole genome association studies: Opportunities and Challenges

1) Understanding genetic architecture of human traits, gene action and disease pathophysiology.

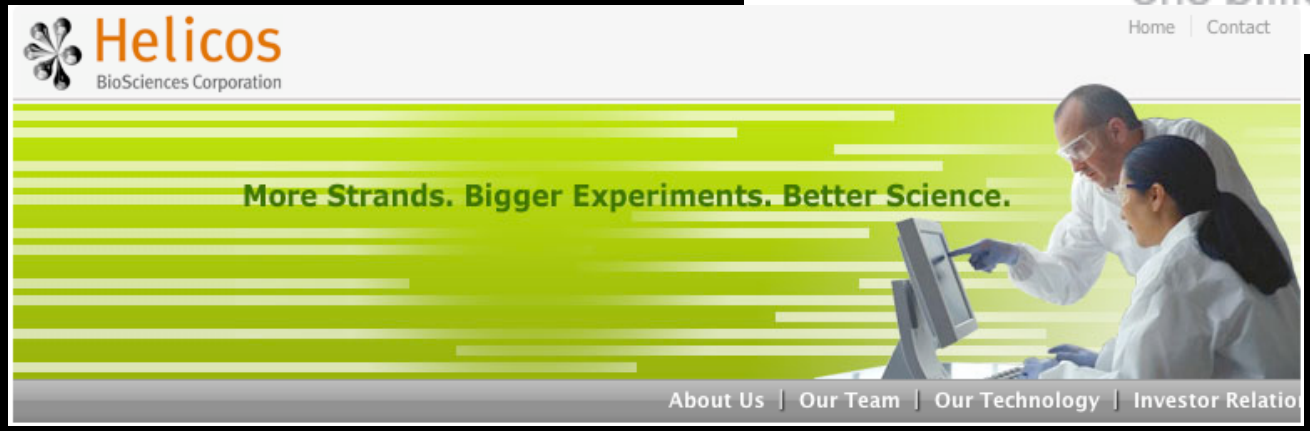
2) Improvement of computational methods for gene discovery.

3) Detecting gene-gene and gene-environment interactions.

4) Replication of results; sharing of results, data and biological samples.

5) Finding the causative variants.

DNA Sequencing Revolution



Prospects of Personalized Medicine

1) Does not need to be universal but should cover the greatest risk variation in the commonest of diseases.

2) Increases safety in healthcare?

3) Decreases cost of healthcare?

4) Need for point-of-care diagnostics and counseling.

5) Need sentinel medical examples.

6) Is going to be less "racial" than currently assumed.

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BLOOD TRANSFUSIONS & ABO GENETIC VARIATION